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Schjørring, Olav Lilleholt; Rasmussen, Bodil Steen

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EDITORIAL

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# The paramount parameter: arterial oxygen tension versus arterial oxygen saturation as target in trials on oxygenation in intensive care

Olav Lilleholt Schjørring<sup>1,2\*</sup>  and Bodil Steen Rasmussen<sup>1,2</sup> 

**Keywords:** Oxygen inhalation therapy, Hyperoxia, Hypoxia, Intensive care units, Respiratory insufficiency, Critical illness

## Main text

Oxygenation targets in critically ill patients admitted to the intensive care unit (ICU), in particular in patients with acute hypoxaemic respiratory failure, are still a matter of debate. There is mounting evidence for potential harm through hyperoxia [1–3]. Nevertheless, the optimal oxygenation targets, which minimise hyperoxia while maintaining sufficient oxygenation to avoid harm through hypoxia, remain unclear. Therefore, larger randomised clinical trials on the subject are needed. Several observational studies [4] as well as interventional before-and-after trials [1, 5] and three small randomised controlled trials [2, 3, 6] have added valuable, although not definitive, evidence to the field. Arterial oxygen saturation (SaO<sub>2</sub>) or pulse oximetry (SpO<sub>2</sub>) has been the primary parameter defining the target range in most of the interventional studies conducted. We would like to dispute this preference of SaO<sub>2</sub> and SpO<sub>2</sub> over arterial oxygen tension (PaO<sub>2</sub>) as the target parameter. Hence, this proposition for debate.

The general hypothesis of the studies on oxygen use in the ICU is that the dangers of oxygen toxicity are underestimated, and that the negative impact of hyperoxia is significant, even when compared to the risks of hypoxia following conservative oxygenation strategies [1, 2, 5, 6]. Hence, studies proposing more conservative oxygenation targets have been conducted primarily in the effort to

avoid hyperoxia. The parameters PaO<sub>2</sub> and SaO<sub>2</sub> are linked as visualised in the oxygen dissociation curve [7]. The interval of PaO<sub>2</sub> in ICU patients spans upwards from approximately 7.3 kPa (55 mmHg) [8–10]. In this area, the oxygen dissociation curve is rather flat [7] and covers only a small range of SaO<sub>2</sub> values. The SaO<sub>2</sub> range becomes even narrower with hyperoxaemic levels of PaO<sub>2</sub> depending on its definition, which varies from over 13.3 kPa (100 mmHg) to over 64.9 kPa (487 mmHg) [4], while the corresponding SaO<sub>2</sub> encompasses only four numeric values from 97% to 100%. This limits the control of hyperoxaemia if SaO<sub>2</sub> is used as the target parameter of oxygenation. Furthermore, when SaO<sub>2</sub> defines the oxygenation target in clinical trials, the narrow SaO<sub>2</sub> spectrum will likely result in a larger risk of an overlap of PaO<sub>2</sub> or SaO<sub>2</sub> between the conventional and interventional study groups.

One could argue that the use of SaO<sub>2</sub> over PaO<sub>2</sub> offers the possibility to use the non-invasive measurement of oxygenation, SpO<sub>2</sub>. The correlation between SaO<sub>2</sub> and SpO<sub>2</sub> is generally high which makes SpO<sub>2</sub> invaluable in the continuous monitoring and titration of oxygen supplementation in the ICU [11]. Nevertheless, SpO<sub>2</sub> is unreliable as a measure of arterial oxygenation in patients with sepsis [12], in patients with use of vasopressors [13], in patients with high or low body temperature [11], and in patients with hypoxaemia [12, 13]. Therefore, SpO<sub>2</sub> cannot be used in the ICU without intermittent measurements of SaO<sub>2</sub> for comparison as remarkable differences above 4.4 percentage points [11] may occur. Furthermore, SpO<sub>2</sub> has been shown inadequate in identifying and in quantifying hyperoxaemia defined as PaO<sub>2</sub> above 16.7 kPa (125 mmHg) at SpO<sub>2</sub> levels

\* Correspondence: [o.schjoerring@rn.dk](mailto:o.schjoerring@rn.dk)

<sup>1</sup>Department of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark

<sup>2</sup>Department of Clinical Medicine, Aalborg University, Søndre Skovvej 15, 9000 Aalborg, Denmark



above 96% [14]. Thus, targeting normoxaemic oxygenation levels in the upper part of the normal reference interval by using SpO<sub>2</sub> would inarguably lead to episodes of definitive hyperoxaemia. Moreover, at the steep slope of the oxygen dissociation curve [7], where the differentiation in SaO<sub>2</sub> is the highest, SpO<sub>2</sub> is also inadequate in correctly identifying the oxygenation level in the ICU as SpO<sub>2</sub> above 94% is necessary to avoid a risk of having SaO<sub>2</sub> below 90% [13]. This fact further narrows the spectrum of differentiation when using SpO<sub>2</sub>.

An argument for using SaO<sub>2</sub> over PaO<sub>2</sub> is that under normal, healthy conditions more than 98% of the transported oxygen is bound to haemoglobin [7]. Therefore, SaO<sub>2</sub> in combination with the haematocrit or haemoglobin level represents the most direct parameter for expressing the amounts of oxygen actually carried in the arterial blood whereas PaO<sub>2</sub> is only a secondarily derived parameter. However, the oxygen dissociation curve [7] shows that SaO<sub>2</sub> and PaO<sub>2</sub> are mutually dependent, and so this point remains essentially theoretical. Additionally, with increasing hyperoxaemia SaO<sub>2</sub> loses its value due to the rigid ceiling of SaO<sub>2</sub> at 100%. Furthermore, since the formation of reactive oxygen species is closely linked to the free amounts of oxygen [15] and since the reactive oxygen species contribute importantly to the detrimental effects of hyperoxia [15], PaO<sub>2</sub> is probably the parameter with the tightest relationship to the toxic properties of oxygen. As these toxic properties are what trials on the subject strive to minimise, one could claim that this connection is just as important as the link between SaO<sub>2</sub> and the total oxygen content of the blood.

In clinical practice, both SaO<sub>2</sub> and PaO<sub>2</sub> are commonly used to guide oxygen therapy, particularly in the ICU setting, as the majority of acute critically ill ICU patients require arterial cannulation for haemodynamic monitoring. For evaluating arterial oxygenation, a recent survey of northern European ICU physicians has shown that PaO<sub>2</sub> was preferred to SaO<sub>2</sub> [16].

In summary, to define the oxygenation target levels precisely, to reduce the risk of unwanted hyperoxaemia, and to minimise overlap between conventional and interventional groups, in clinical trials of higher versus lower oxygenation targets in the ICU population, PaO<sub>2</sub> is in our opinion the superior target parameter as compared to SaO<sub>2</sub>. This is also reflected in clinicians' self-reported preferences. Therefore, we advocate the use of PaO<sub>2</sub> as the primary target parameter of arterial oxygenation in future clinical trials that aim to establish the evidence of how to use medical oxygen in patients admitted to the ICU.

#### Abbreviations

HOT-ICU: Handling Oxygenation Targets in the Intensive Care Unit; ICU: Intensive care unit; PaO<sub>2</sub>: Arterial oxygen tension; SaO<sub>2</sub>: Arterial oxygen saturation; SpO<sub>2</sub>: Pulse oximetry

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#### Authors' contributions

BSR conceived the idea for the editorial. OLS drafted the primary manuscript. OLS and BSR revised the manuscript together. Both authors have read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

Both authors are involved in an ongoing investigator-initiated randomised trial targeting oxygenation in acutely ill patients in the ICU, the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (ClinicalTrials.gov NCT03174002), OLS as coordinating investigator and BSR as sponsor and primary investigator.

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